

GIST LEARN Online: Aug. 15, 2020

GIST Updates - based on selected presentations by the clinicians and researchers at LifeFest, July 2020 (full recordings of the presentations are available on Youtube)



David Josephy  
Life Raft Group Canada

[david.josephy@liferaftgroup.ca](mailto:david.josephy@liferaftgroup.ca)

***Disclaimer: I am not a physician. I am a scientist (biochemistry/ toxicology) with some experience in cancer research.***

***Nothing in this presentation should be regarded as medical advice or as a substitute for consulting with your doctors.***

# Life Fest 2020: Clinical updates

A screenshot of a Zoom meeting grid for 'Life Fest 2020: Clinical updates'. The grid consists of six video thumbnails arranged in two rows of three. Each thumbnail has a name label at the bottom. The participants are:

- Top-left: Diana Nieves (woman with glasses, blue shirt)
- Top-middle: Dr. Breeilyn Wilky (woman, background: 'Present and conquer cancer. Together.' with mountains)
- Top-right: Dr. Alan Livingstone (man, light blue shirt)
- Bottom-left: Dr. Jonathan Trent (man in a hat, background: beach scene)
- Bottom-middle: Dr. Arun Singh (man with headset, background: beach scene)
- Bottom-right: Dr. Gina D'Amato (woman, background: 'VIRTUAL LIFE FEST 2020 Friday, 13th')

The Zoom player interface at the bottom includes a red progress bar, a play button, a volume icon, and a timestamp of 47:23 / 1:36:01. The Zoom logo is visible in the bottom right corner of the player area.

Dr. Breelyn Wilky, U. of Colorado

Updates on GIST treatment

Adjuvant imatinib: clinical trial update:

3-year adjuvant treatment reduces risk of recurrence and improves overall survival - the benefit persists all the way out to 10 years.

What about adjuvant therapy for longer than 3 years?  
Clinical trials are ongoing - no data yet.

# Wilky: Metastatic GIST therapies

2020 is a “glorious year” for GIST patients!

There are now five drugs FDA-approved for GIST: the familiar three (imatinib, sunitinib, regorafenib); and now avapritinib and ripretinib, both specifically developed for GIST;

Plus, a handful of other drugs have been shown to be effective (off-label): pazopanib (Votrient); dasatinib (Sprycel); nilotinib (Tasigna), sorafenib (Nexavar).

Mutation analysis - from either a tumor biopsy or a “liquid biopsy” (ctDNA from blood plasma) is extremely important to guide the decision as to which treatment is best.

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**Dr. Jon Trent, U. of Miami Sylvester Cancer Center**

**Mutational testing and ctDNA studies**

## Trent: GIST subtypes and their treatment

*Mutation testing is required for optimal treatment of GIST patients.*

- |                         |  |
|-------------------------|--|
| 1. KIT exon 11          | imatinib 400 mg                                  |
| 2. KIT exon 9           | imatinib 800 mg (or tolerated dose)              |
| 3. PDGFR $\alpha$ D842V | avapritinib                                      |
| 4. SDH-deficient        | sunitinib or regorafenib<br>(temozolomide trial) |
| 5. Raf V600E            | Raf inhibitor                                    |
| 6. Nf-1, Ras            | Raf or Mek inhibitor                             |
| 7. PI3K                 | mTOR inhibitor                                   |
| 8. IGF-1R-expressing    | IGF-1R inhibitor trial                           |
| 9. TRK fusion           | larotrectanib                                    |

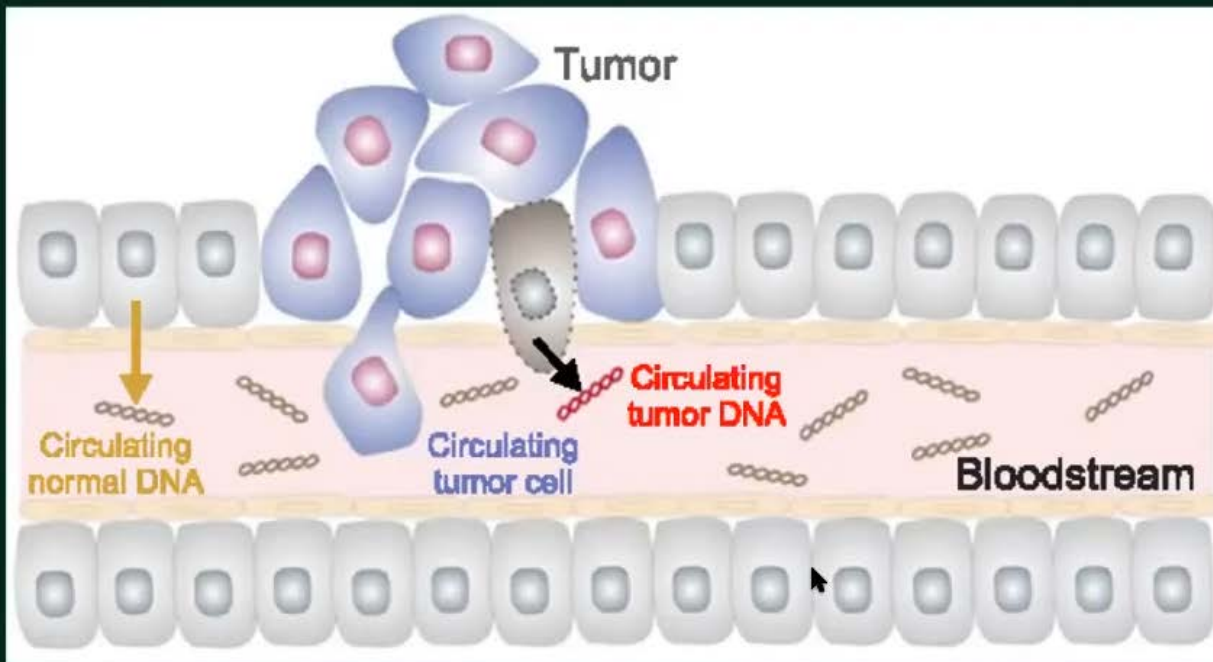
### KIT resistance mutations:

- |                            |                           |
|----------------------------|---------------------------|
| exon 13 (ATP binding site) | sunitinib 37.5 mg         |
| exon 17 (Activation loop)  | regorafenib or ripretinib |

# Trent: ctDNA studies



## Circulating Tumor DNA Mutation Testing From Blood (Liquid Biopsy)



Nurwidya et al, 2018  
Bauer JCO 2015  
Serrano BJC 2018



7:1:36:01



# Sylvester ctDNA Study



- IRB-approved protocol
- Analysis of **243 GIST patients**
- Patient data extracted then stored in a HIPPA compliant database
- ctDNA on blood samples
- NGS sequencing performed on blood (ctDNA) and tumor (FFPE)



## Trent: ctDNA: Conclusions

ctDNA analysis is a useful, noninvasive method to understand resistance mutations in GIST patients.

*ctDNA is the future of mutation testing*, but we need to improve its sensitivity and to validate the concept of using ctDNA to guide therapy.

Dr. Gina D'Amato, U. of Miami

New, recently approved treatments:

BLU-285/ avapritinib (Ayvakit; Blueprint): specific for KIT/ PDGFRA

NAVIGATOR trial July 2020; PDGFRA D842V mutant GIST; 89% response

300 mg daily

VOYAGER 3<sup>rd</sup> line trial - avapritinib did not beat regorafenib

ripretinib (QINlock; Deciphera): "it works great";  
approved for use after the three lines have been tried.

150 mg daily

## *Research updates*

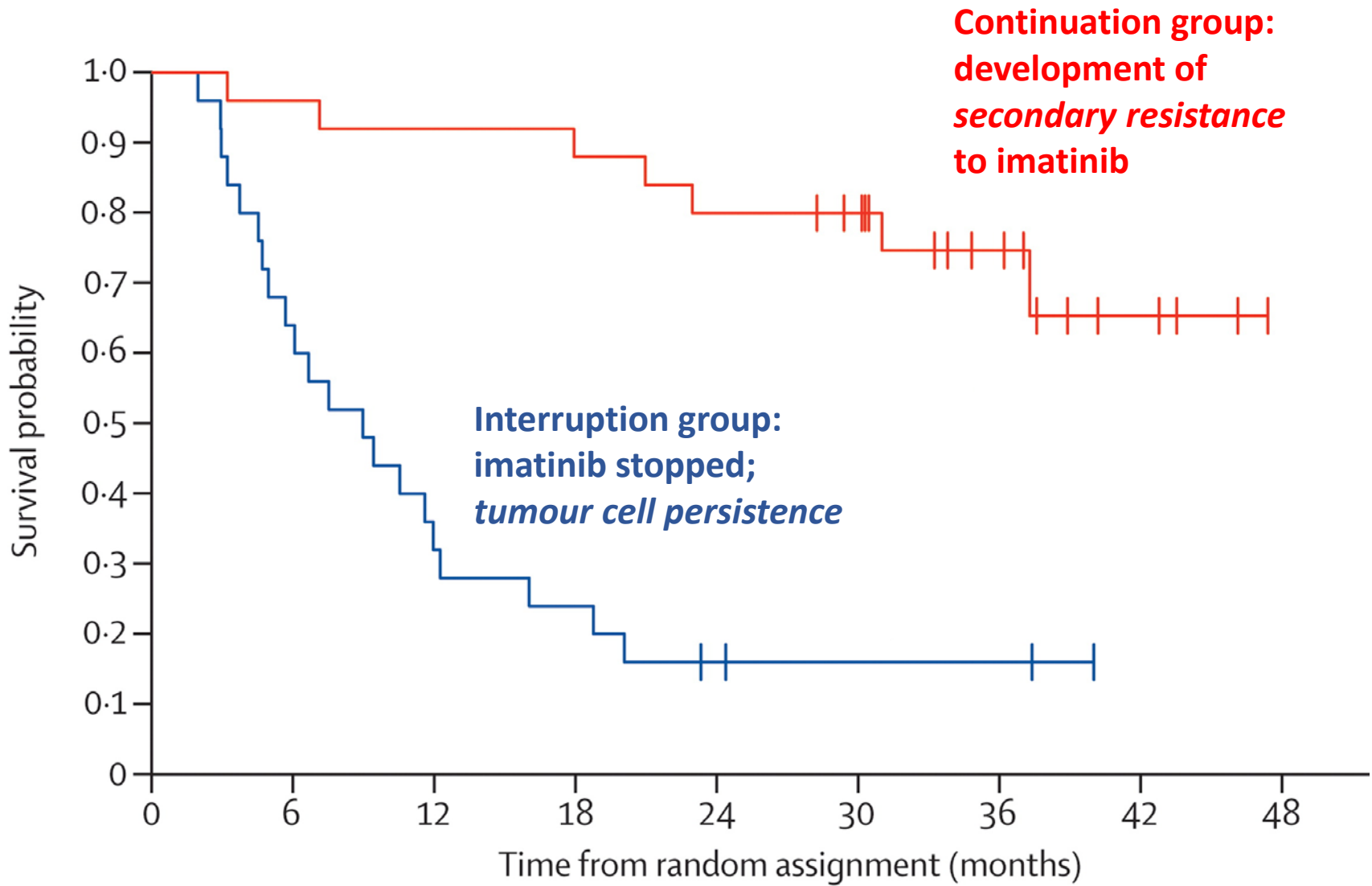
Dr. Michael Heinrich (OHSU, Oregon)

### 1. Modeling quiescence/ persistence in GIST

#### *Background:*

Reviewed the French clinical trial (2010) of *stopping* imatinib therapy after 3 years.

The question needed to be asked: Should metastatic GIST patients keep taking imatinib indefinitely? The French trial provided the answer: "Yes".



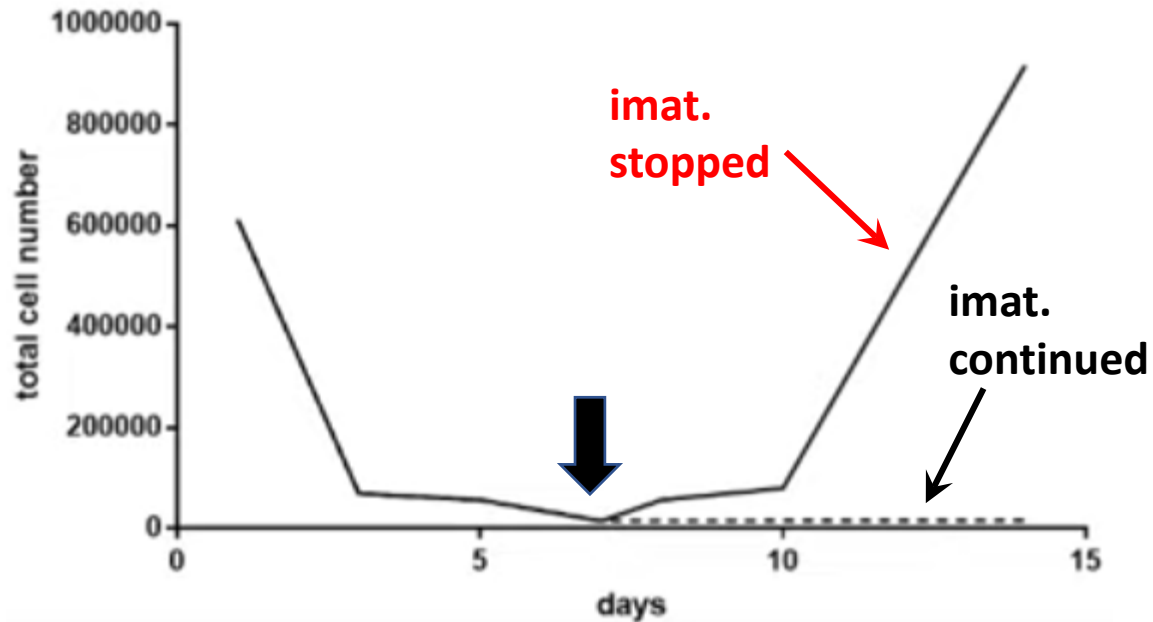
**Le Cesne *et al.*, Discontinuation of imatinib in patients with advanced GIST after 3 years of treatment; French Sarcoma Group, *Lancet Oncol.* 2010**

*Conclusions from the French clinical trial:*

Imatinib does not cure GIST; some cells persist in a quiescent/dormant state; when imatinib is stopped, the cells soon start growing again.

Note that the dormant cells are still sensitive to imatinib, and disease control was regained once imatinib treatment was resumed.

# Heinrich lab study: *in vitro* modelling of GIST persistence



*Looking for a drug therapy to apply to the “dormant” GIST cells ...*

Heinrich:

## 2. Constructing a PDGFR $\alpha$ D842V GIST cell line

No-one has succeeded in culturing a PDGFR $\alpha$ -mutant GIST cell line.

*Strategy:* Start with GIST-T1 (*KIT*-mutant) cells: using CRISPR technology: put in the PDGFR $\alpha$  mutation and then take out the *KIT* mutation.

The resulting cells are sensitive to avapritinib but not to imatinib.

Can use this cell line to test new drugs; lab has already identified several candidate compounds.